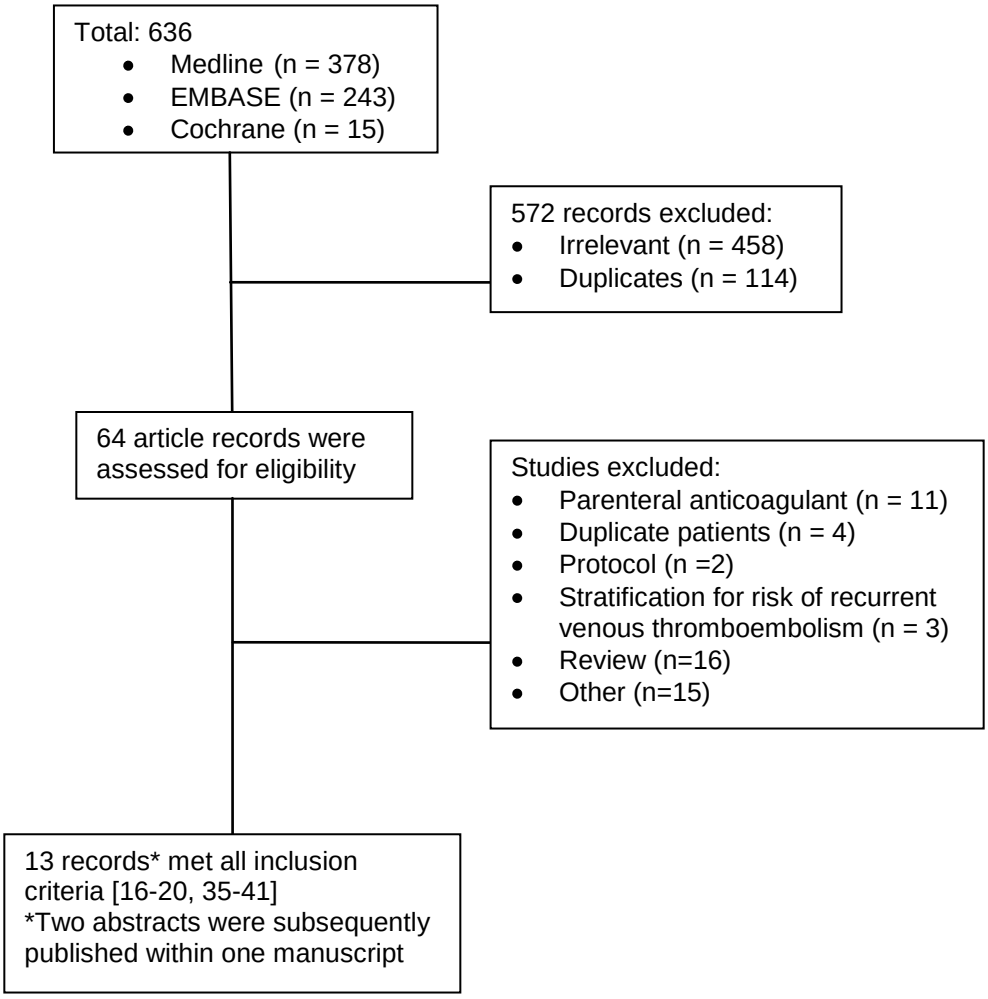
Web appendix: Supplementary material

Appendix 1 (on-line): Medline search strategy

exp Venous Thrombosis/
Deep vein thrombosis.mp.
Pulmonary embolism.mp. or exp Pulmonary Embolism/
recurrent venous thromboembolism.mp.
exp Warfarin/
exp Acenocoumarol/
oral anticoagulant.mp.
Ximelagatran.mp.
Direct thrombin inhibitor.mp.
dabigatran.mp.
rivaroxaban.mp.
apixaban.mp.
direct Xa inhibitor.mp.
exp Aspirin/ or ASA.mp.
Pradax$.mp.
xarelto.mp.
eliquis.mp.
coumadin.mp.
randomized controlled trial.pt.
controlled clinical trial.pt.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/18-22
clinical trial.pt.
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
exp Acenocoumarol/

Appendix 2 (on-line): Flow Diagram summarizing the identification process of relevant clinical trials



Appendix 3 (on-line): Study Quality

Study, Year (Reference)	Adequate Sequence Generation?	Allocation Concealment?	Blinding?	Incomplete Outcome Data Addressed?	Free of Selective Outcome Reporting?	Free of Other Bias?
DURAC 2 [35]	Yes	Yes	No	Yes	Yes	Yes
LAFIT [36]	Yes	Yes	Yes	Yes	Yes[a]	Yes
WODIT DVT [37]	Yes	Unclear	Yes[b]	Yes	Yes[c]	Yes
WODIT PE [40]	Yes	Unclear	Yes[b]	Yes	Yes[c]	Yes
ELATE [39]	Yes	Yes	Yes	Yes	Yes	Yes
PREVENT [38]	Yes	Yes	Yes	Yes	Yes[a]	Yes
Thrive III [41]	Yes	Yes	Yes	Yes	Yes	Yes[d]
RESONATE [20]	Yes	Yes	Yes	Yes	Yes	Yes[d]
REMEDY [20]	Yes	Yes	Yes	Yes	Yes	Yes[d]
EINSTEIN-EXT [16]	Yes	Yes	Yes	Yes	Yes	Yes[d]
AMPLIFY-EXT [19]	Yes	Yes	Yes	Yes	Yes	Yes[d]
WARFASA [17]	Yes	Yes	Yes	Yes	Yes[e]	Yes
ASPIRE [18]	Yes	Yes	Yes	Yes	Yes	Yes

a: trial stopped early based on evidence of efficacy; b: open label but blinded outcome assessment; c: trial stopped early based on interim analysis showing minimal difference between groups; d: sponsor performed data analysis but data available to authors; e: 2 protocol amendments were made

Appendix 4 (on-line):

Bayesian network meta-analysis allows the analyst to estimate the probability that a treatment is best, second best, and so on for a particular outcome.

Probability Best Therapy (%)

Treatment	Recurrence of VTE	Major Bleeding
Placebo/Observation	0.0%	1.36%
Standard Adjusted-Dose VKA	66.2%	0.00%
ASA 100 mg daily	0.0%	2.48%
Dabigatran 150 mg twice daily	16.7%	0.27%
Apixaban 5 mg twice daily	2.3%	69.40%
Apixaban 2.5 mg twice daily	2.9%	22.38%
Rivaroxaban 20 mg daily	5.4%	0.14%
Low-intensity VKA	0.0%	0.02%

mg: milligram; VTE: venous thromboembolism.

A simple numerical summary of these probabilities – the surface under the cumulative ranking (SUCRA) – for each treatment can also be calculated [50]. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. For example, for recurrent VTE, the SUCRA value for standard adjusted dose VKA is 94%, which is better than other treatments. By contrast, placebo/observation has a SUCRA of 0% for recurrent VTE, meaning it is certain to be worst for this outcome.

Surface under the cumulative ranking (SUCRA) values (%)

Treatment	Recurrence of VTE	Major Bleeding
Placebo/Observation	0%	68%
Standard Adjusted-Dose VKA	94%	17%
ASA 100 mg daily	13%	59%
Dabigatran 150 mg twice daily	82%	39%
Apixaban 5 mg twice daily	54%	93%
Apixaban 2.5 mg twice daily	55%	82%
Rivaroxaban 20 mg daily	56%	8%
Low-intensity VKA	33%	22%

SUCRA: Surface under the cumulative ranking curve; mg: milligram; VTE: venous thromboembolism.

Appendix 5 (on-line): Direct, frequentist, meta-analysis of recurrent VTE and major bleeding events

Oral Anticoagulants or Antiplatelet Agents versus Placebo	Reports, n	Recurrent VTE OR (95% CI) vs. placebo	Major Bleeding OR (95% CI) vs. placebo
Standard adjusted-dose VKA	2†	0.06 (95% CI: 0.02-0.27; I^2=0%)	5.74 (95% CI: 1.26-26.1; I^2=0%)
ASA 100 mg daily	2	0.66 (95% CI: 0.46-0.93; I^2=16.5%)*	1.28 (0.47-3.48; I^2=0%)
Dabigatran 150 mg twice daily	1	0.07 (95% CI: 0.02-0.23)	4.94 (95% CI: 0.23-105.11)
Apixaban 5 mg twice daily	1	0.18 (95% CI: 0.1-0.32)	0.25 (95% CI: 0.03-2.25)
Apixaban 2.5 mg twice daily	1	0.18 (95% CI: 0.1-0.32)	0.49 (95% CI: 0.09-2.7)
Rivaroxaban 20 mg daily	1	0.18 (95% CI: 0.08-0.39)	9.01 (95% CI: 0.48-170.43)
Low-intensity VKA	1	0.34 (95% CI: 0.18-0.65)	2.51 (95% CI: 0.48-13.02)

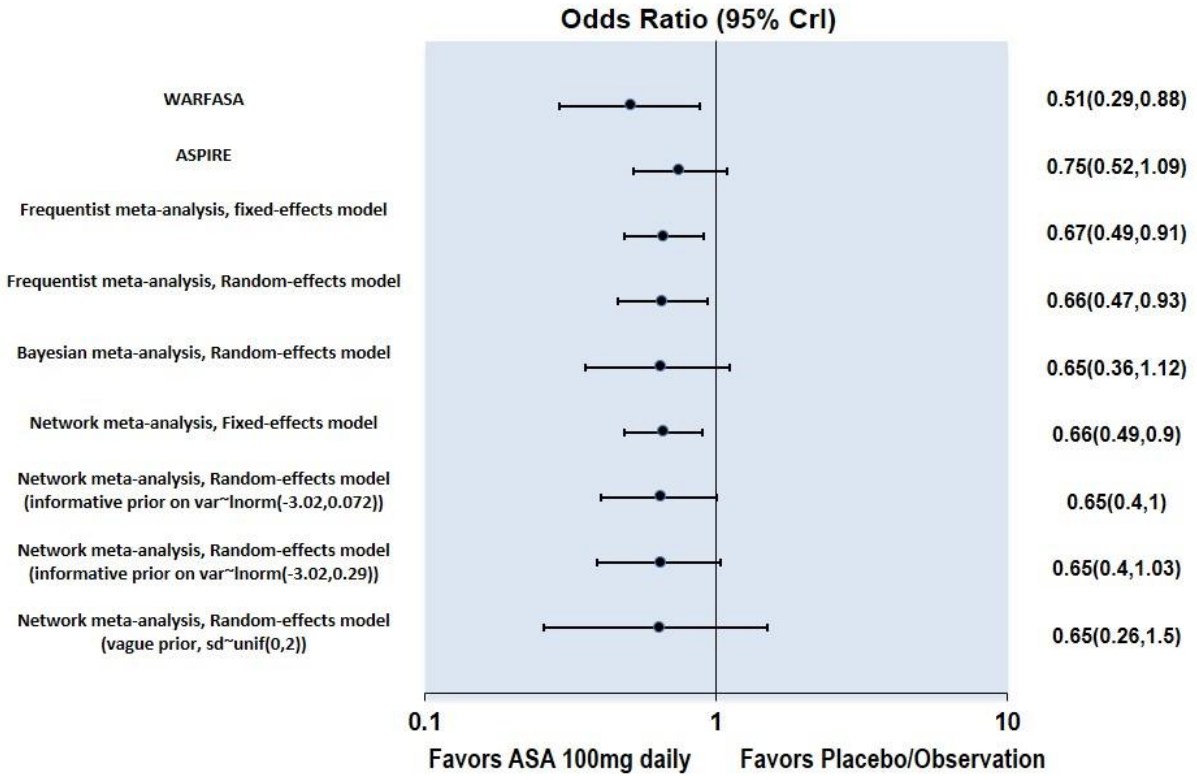
CI: confidence intervals; mg: milligram; OR: odds ratio; VTE: venous thromboembolism

† 3 RCTs for Major Bleeding

* Direct estimates reported here are derived from frequentist meta-analysis where between studies variance is treated as a constant. In direct Bayesian network meta-analysis, the credible intervals are wider than confidence intervals because uncertainty around between study variance is incorporated into the estimates. Consequently, Bayesian estimates for direct comparisons of ASA versus placebo may cross one depending on the choice of prior (see Appendix 6)

Appendix 6 (on-line): Summary of analyses to support choice of model and prior for between study variance for network meta-analyses

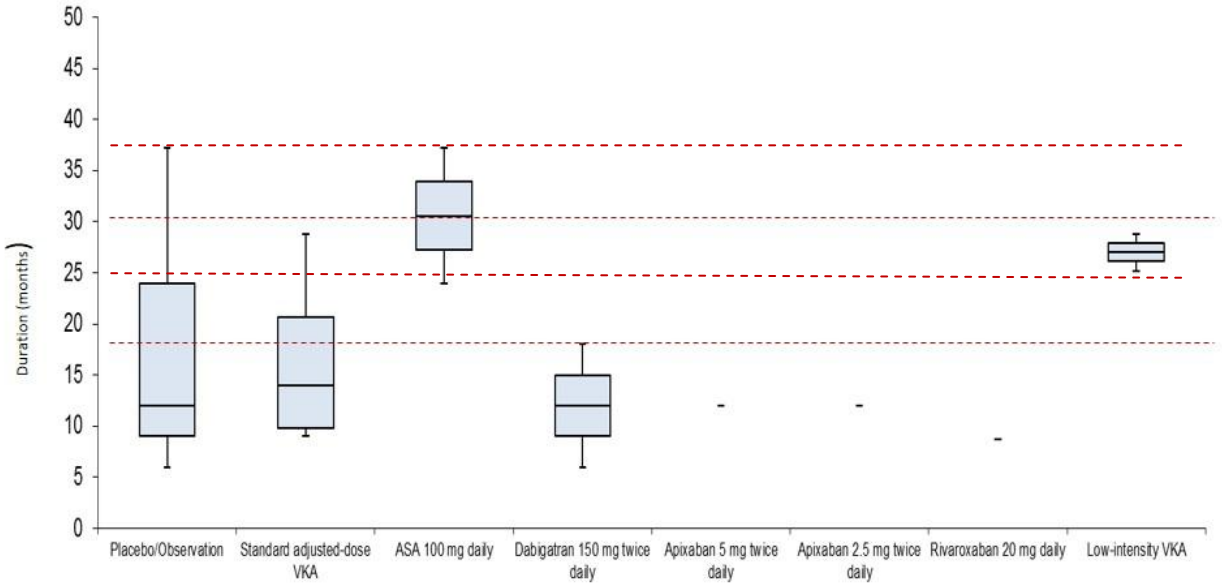
We conducted a number of analyses to assess the efficacy of ASA versus placebo for recurrent VTE (Figure) and results were sensitive to choice of analysis. Two trials comparing ASA to placebo. ASA was associated with a statistically significant reduction versus placebo in WARFASA but not in ASPIRE. When pooling these studies together using classical (or frequentist) pair-wise meta-analysis techniques, ASA was associated with a statistically significant reduction in recurrent VTE relative to placebo. However, in frequentist meta-analysis, the between study variance is treated as a constant [51]. Consequently, frequentist meta-analyses may not accurately reflect uncertainty around effect estimates thereby narrowing the width of the confidence intervals. By contrast, between study variance in a Bayesian analysis is treated as a distribution (as opposed to a constant), reflecting uncertainty around this parameter. Accordingly, the credible intervals are wider for the Bayesian meta-analysis of WARFASA and ASPIRE. For the network meta-analysis, we considered a number of models: fixed-effects model, random-effects model using an informative prior on the heterogeneity variance [28;29], and a random-effects model using vague priors (sd~dunif(0,2)). For the reference case, we opted to use the random-effects model using an informative prior on the heterogeneity variance. This model is recommended when there are a small number of trials in evidence networks [28;29],and is based on empirical data from the Cochrane Database of Systematic Reviews. All of the models fit the data reasonably well, but the residual deviance was lower (21.32) for the random-effects model using the informative prior than the fixed-effect network meta-analysis (21.57) and random-effects network meta-analysis using vague priors (21.45). The results for the model using informative priors fell between those reported for the fixed-effects model and the random-effects model using a vague prior on the heterogeneity variance (sd~dunif(0,2)). We also ran sensitivity analyses exploring how sensitive the credible intervals are if you change the precision of the above lognormal prior to 0.29/4=0.072. The results were sensitive to this parameter and the upper bound of the credible interval approached unity. Detailed results for all treatments for fixed and random-effects network meta-analyses using vague priors (sd~dunif(0,2)) are reported in Appendix 12.


Odds Ratio (95% CrI)
WARFASA
ASPIRE
Frequentist meta-analysis, fixed-effects model
Frequentist meta-analysis, Random-effects model
Bayesian meta-analysis, Random-effects model
Network meta-analysis, Fixed-effects model
Network meta-analysis, Random-effects model (informative prior on var~lnorm(-3.02,0.072))
Network meta-analysis, Random-effects model (informative prior on var~lnorm(-3.02,0.29))
Network meta-analysis, Random-effects model (vague prior, sd~unif(0,2))
0.51(0.29,0.88)
0.75(0.52,1.09)
0.67(0.49,0.91)
0.66(0.47,0.93)
0.65(0.36,1.12)
0.66(0.49,0.9)
0.65(0.4,1)
0.65(0.4,1.03)
0.65(0.26,1.5)
0.1
1
10
Favors ASA 100mg daily
Favors Placebo/Observation

Appendix 7 (on-line): Sensitivity analysis for duration of study

The studies including ASA (ASPIRE, WARFASA) and low intensity VKA (ELATE, PREVENT) were longer in duration than those for other treatments (Figure A7).

Figure A7: Box plot comparing treatments by study duration



We conducted a subgroup analysis to examine whether duration of treatment may have impacted results. A meta-regression was considered but yielded unreliable results because the network was comprised largely of single study connections. For the subgroup analysis, we considered studies that were within 6 months duration of shortest ASA trial – WARFASA. Only 4 studies (REMEDY, ASPIRE, ELATE, and PREVENT) were between 18 and 30 months in duration; the treatments within these studies included placebo, ASA, adjusted dose VKA, dabigatran, and low-intensity VKA in the evidence network. Studies containing apixaban and rivaroxaban were shorter than 18 months in duration.

We conducted a fixed-effects network meta-analysis because all connections within the subgroup analysis were comprised of single study connection. A comparison of results from with subgroup analysis with the primary analysis is provided in Table A7. The results for ASA are slightly more favourable in the subgroup analysis (OR 0.51 (95% CrI: 0.29-0.88)) compared with the primary analysis (OR 0.65 (95% CrI: 0.39-1.03)). However, the effect estimates for ASA remain less pronounced compared with the other

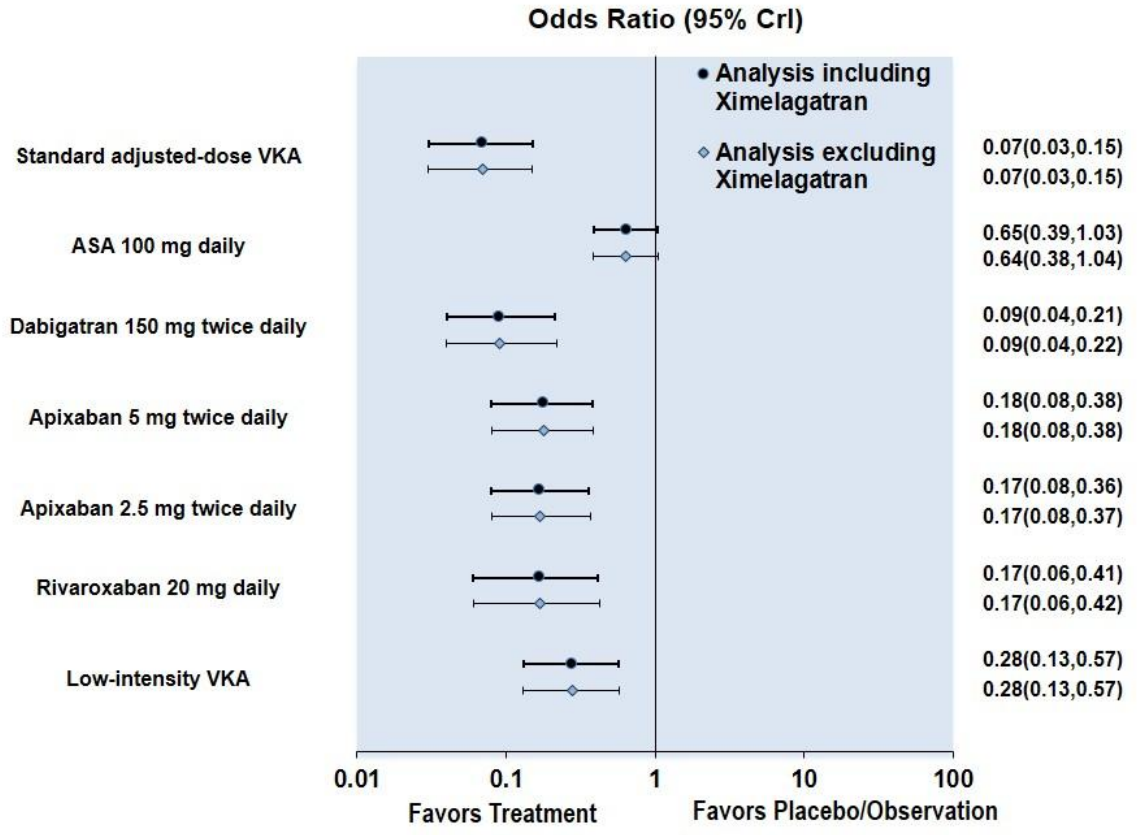
treatments that remain. The ordering of ASA in terms of benefit for prevention of recurrent venous thromboembolism remained the same – better than placebo but worse than low-intensity VKA, dabigatran, and standard adjusteddose VKA. This is reflected in the surface under the cumulative ranking curve (SUCRA) values [50]. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. The ordering of SUCRA values in the subgroup analysis were similar to those in the primary analysis. Aspirin has higher values (31%) than placebo (0%), but lower values compared to low-intensity VKA (49%), dabigatran (73%), and standard adjusted dose VKA (97%).

Table A7: Comparison of results from primary analysis and sub-group analysis for study duration

Treatment	Primary Analysis		Sub-group analysis	
	Recurrent VTE OR (95% CrI) vs. placebo	**SUCRA**	**Recurrent VTE OR (95% CrI) vs. placebo**	**SUCRA**
Placebo/Observation	Reference	0%	Reference	0%
Standard Adjusted-Dose VKA	0.07(0.03,0.15)	94%	0.12(0.03,0.36)	97%
ASA 100 mg daily	0.65(0.39,1.03)	13%	0.51(0.29,0.88)	31%
Dabigatran 150 mg twice daily	0.09(0.04,0.21)	82%	0.17(0.04,0.61)	73%
Apixaban 5 mg twice daily	0.18(0.08,0.38)	54%	NA	NA
Apixaban 2.5 mg twice daily	0.17(0.08,0.36)	55%	NA	NA
Rivaroxaban 20 mg daily	0.17(0.06,0.41)	56%	NA	NA
Low-intensity VKA	0.28(0.13,0.57)	33%	0.33(0.17,0.62)	49%

CrI: credible intervals; SUCRA: Surface under the cumulative ranking curve;

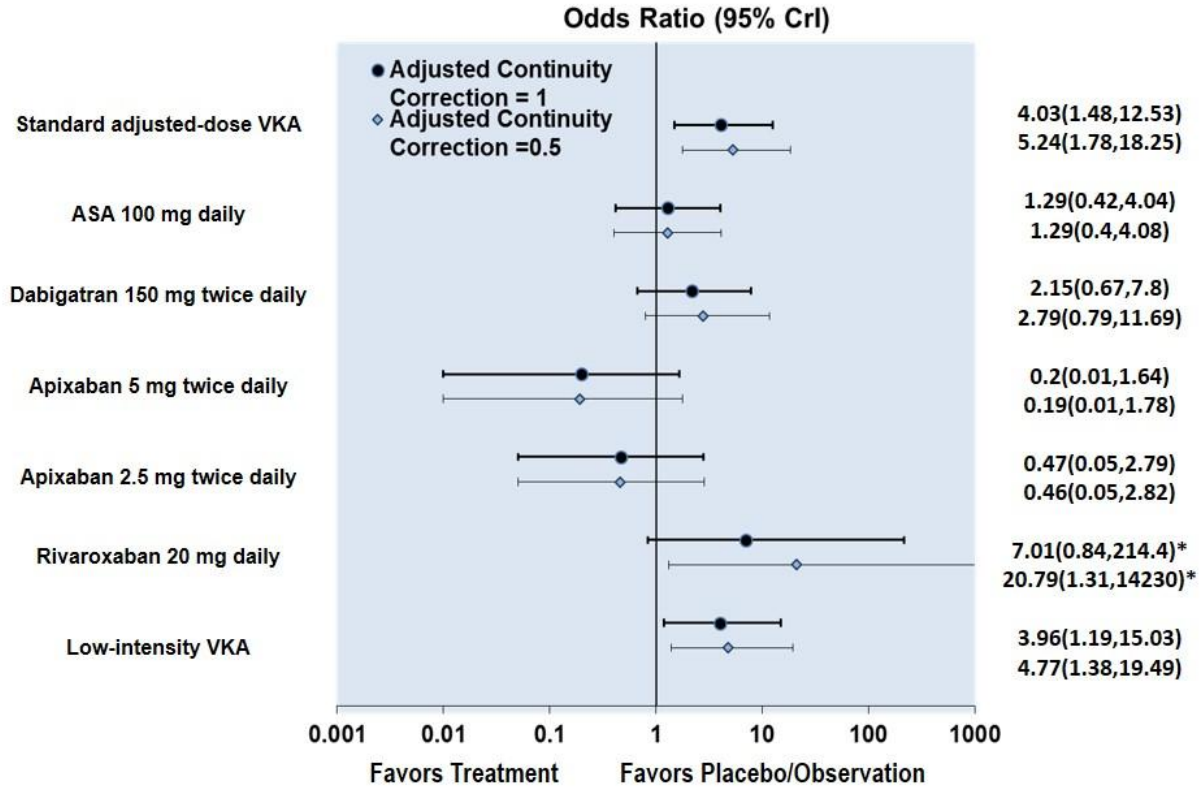
Appendix 8 (on-line): Sensitivity analysis removing ximelagatran from evidence network. Odds ratio (± 95% Credible Interval) for recurrent venous thromboembolism in Bayesian network meta-analysis versus placebo/observation.



CrI= credible interval; mg= milligram

Appendix 9 (on-line): Odds ratio (± 95% Credible Interval) for major bleeding (adjusted continuity correction 0.5 vs. 1) in Bayesian network meta-analysis versus placebo/observation

There was only one study evaluating rivaroxaban for major bleeding and this study contained a zero cell (0/590 in placebo and 4/598 in rivaroxaban) resulting in uncertain estimates of effect. We applied an adjusted continuity correction of 0.5 to account for zero in this study. We also ran a sensitivity analysis where we assumed a continuity correction of 1, which resulted in a less pronounced odds ratio for rivaroxaban. Results for rivaroxaban should be interpreted with caution.



CrI: credible interval; mg: milligram

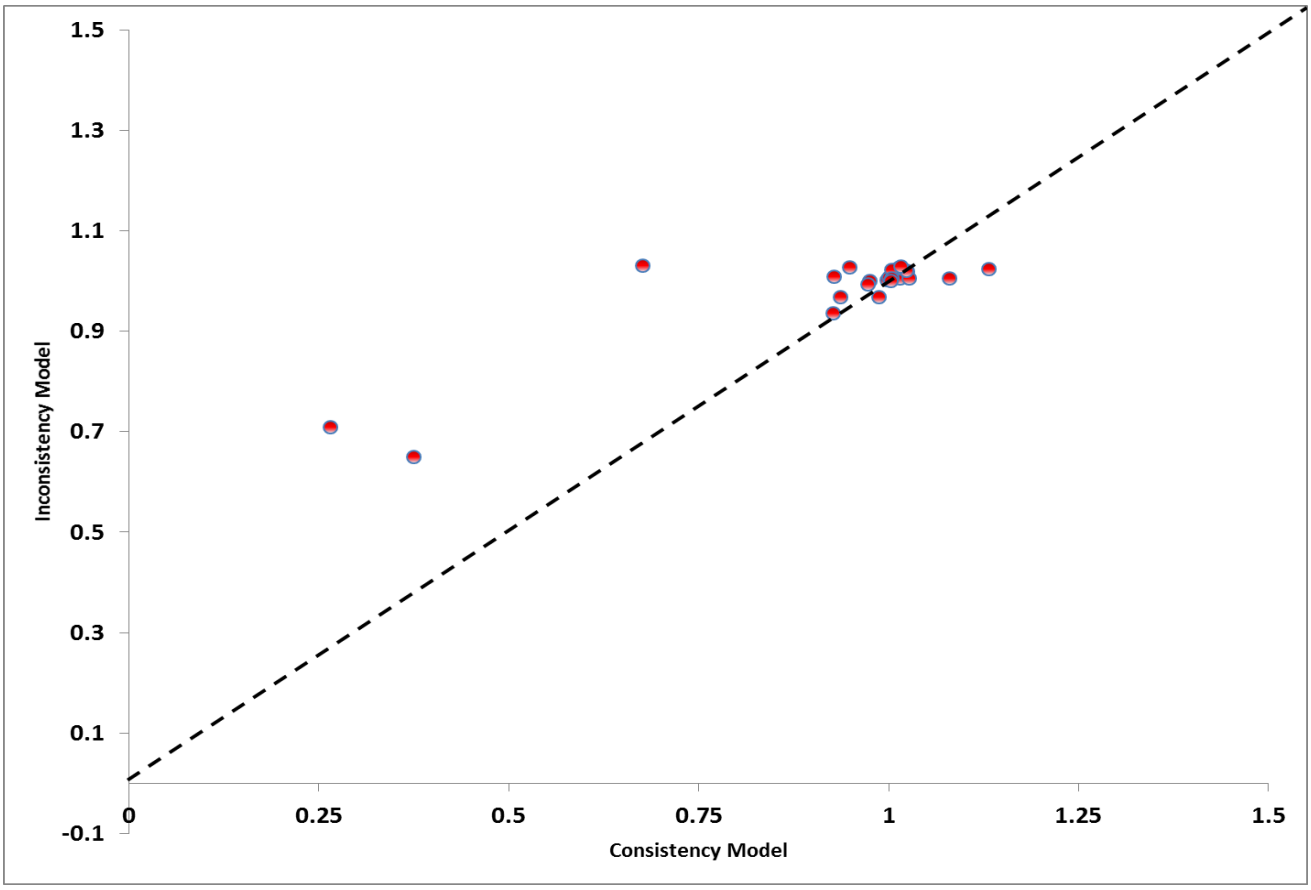
Appendix 10 (on-line): Summary of data for fatal recurrent VTE and fatal bleeding events

Treatment	Fatal recurrent VTE	Fatal bleeding
Placebo/Observation	9/3864	4/3657
ASA 100 mg daily	2/616	0/411
Standard dose VKA	3/2008	1/2098
Low dose VKA	1/624	0/624
Apixaban 5 mg twice daily	0/813	0/811
Apixaban 2.5 mg twice daily	0/840	0/840
Rivaroxaban 20 mg daily	0/602	0/598
Dabigatran 150 mg twice daily	1/2111	0/2114

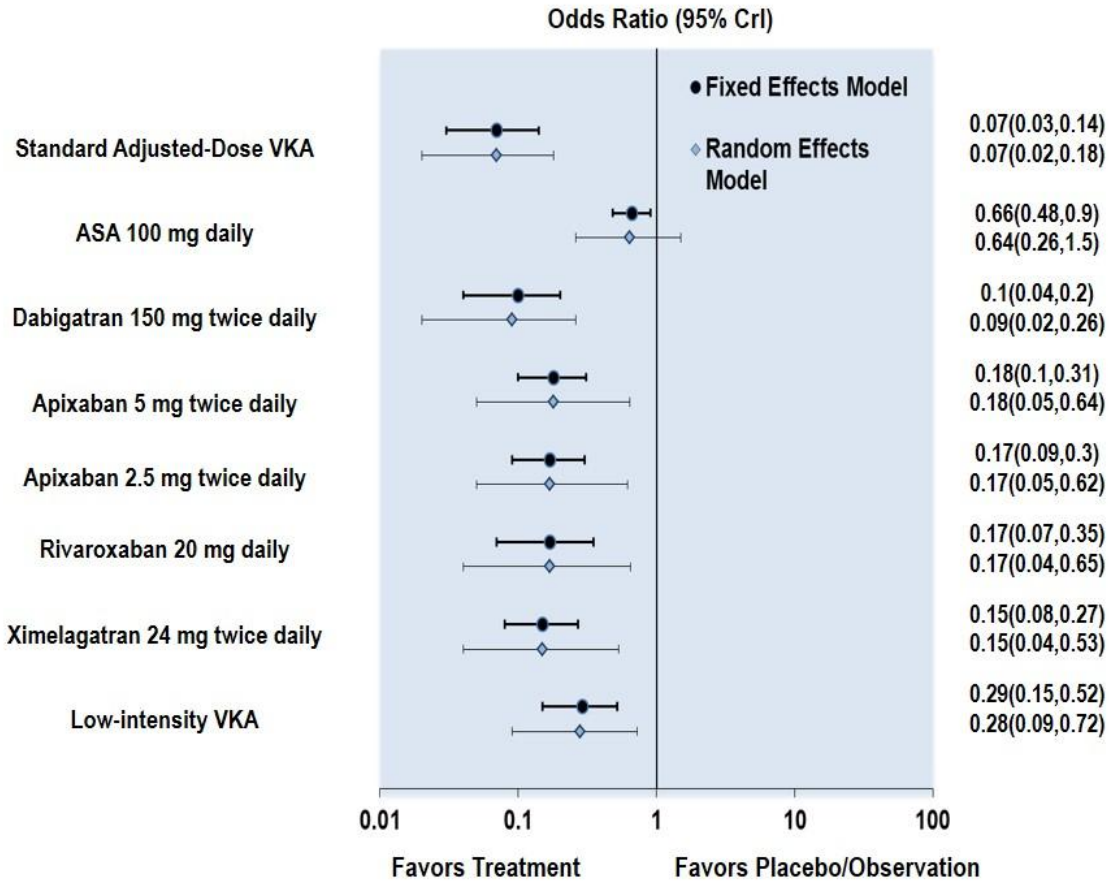
mg: milligram; VTE: venous thromboembolism

Appendix 11 (on-line): Assessment of Inconsistency

We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a lower posterior mean of the residual deviance (21.32 vs. 22.47) and hence is a better fit to the data, although they are very similar for both models. The parameter estimates are also similar for both models and there is considerable overlap in the 95% credible intervals, suggesting no evidence of inconsistency in the network.



Appendix 12 (on-line): Odds ratio (OR) for recurrent venous thromboembolism in Bayesian network meta-analysis versus placebo/observation for fixed-effects model and random-effects model using vague priors (sd~uniform(0,2)). Data points represent the OR ± 95% Credible Interval (CrI).



CrI= credible interval; mg= milligram